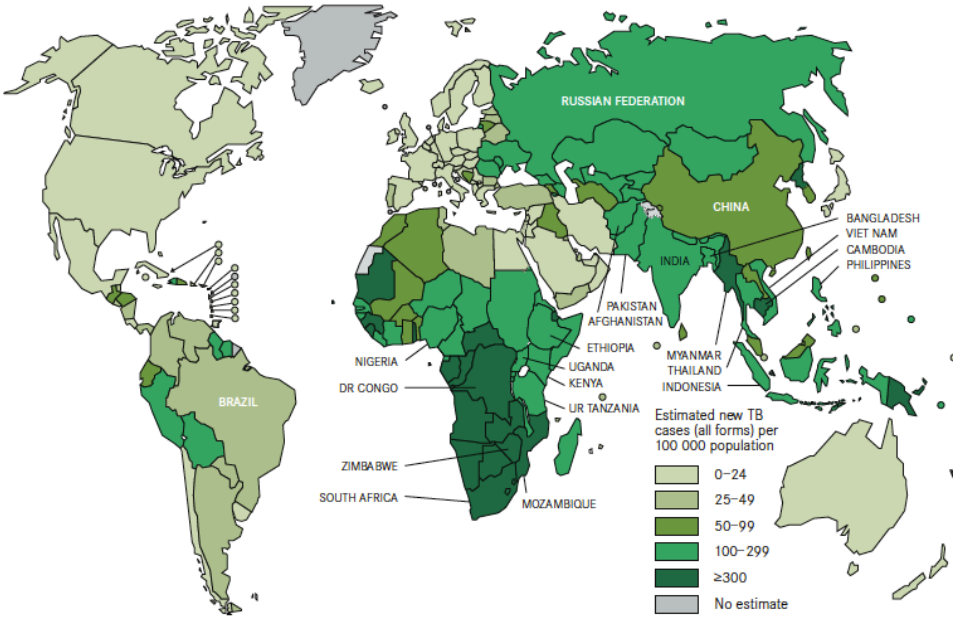
SQ609 for the Treatment of Tuberculosis

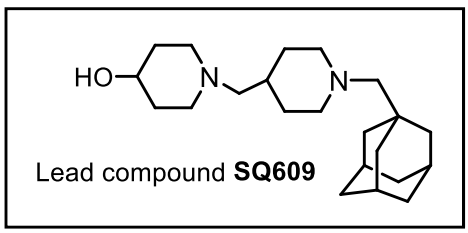
Development Status: Preclinical

Since 2000, Sequella has been focused on discovery of new scaffolds with antimycobacterial activity and development of new drugs for the treatment of tuberculosis (TB). As a result of these studies, we identified novel classes of antitubercular compounds that are structurally distinct and different in mechanism of action from existing TB drugs. A lead compound from one of these novel classes is SQ609, a TB drug candidate with potent and specific activity against both drug-sensitive and drug-resistant forms of *M. tuberculosis* (Mtb), low toxicity, activity in *in vivo* models of Mtb infection, and a favorable safety and pharmacology profile. SQ609 is ready for IND-directed preclinical studies and evaluation in clinical trials.

TB is a public health crisis and unmet medical need. TB is the cause of the largest number of human deaths attributable to a single etiologic agent, killing nearly 2 million people each year. The poor efficacy of existing TB drugs requires that they be administered in a multidrug regimen for at least six months. This results in poor patient compliance and leads to development of multidrug-resistant TB (MDR-TB) and extremely drug-resistant TB (XDR-TB). MDR-TB and XDR-TB are even more difficult to treat (5-8 drugs for up to 24 months) and have significantly higher mortality. Decades of misuse of existing antibiotics and poor compliance have created an epidemic of drug resistance that threatens TB control programs worldwide. New drugs and treatment regimens with activity against drug-susceptible and drug-resistant TB are desperately needed to manage this public health crisis.

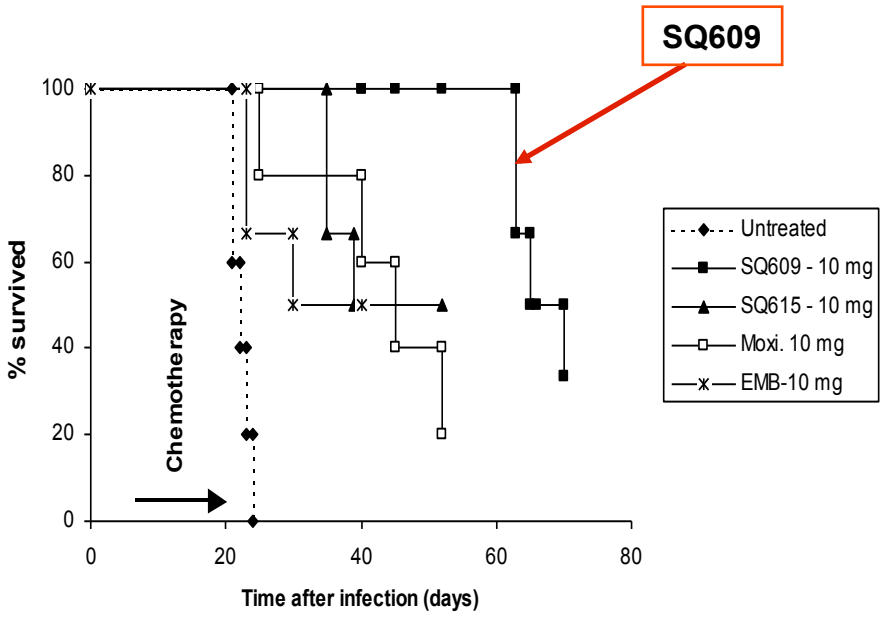


SQ609 has promising activity against drug-susceptible and drug-resistant TB. Sequella identified an intriguing class of anti-TB compounds derived from a 10,240-compound library based on commercially available amino acids and containing a dipiperidine pharmacophore. These compounds demonstrated promising anti-TB activity and had a mechanism that targeted the cell wall of the bacteria.[1] The dipiperidine hits included adamantane-containing hydroxydipiperidine, SQ609, and further studies demonstrated SQ609 to be the most promising compound of its class.[2] It has good *in vitro* activity against a broad range of clinical isolates of Mtb, including strains that are MDR. It shows additive or synergistic activity with all of the first-line TB drugs, suggesting that it could be very efficacious if it were added to or replaced one of the drugs in the first-line regimen.



Lead compound **SQ609**

In a mouse model of TB infection, SQ609 completely prevented Mtb-induced weight loss and improved survival as compared to mice treated with moxifloxicin or ethambutol. This protection continued long after therapy was withdrawn, suggesting that SQ609 has a very prolonged therapeutic effect. In another study, we found that a combination of the standard four drug treatment regimen in which SQ609 replaced ethambutol was more effective at eliminating Mtb from infected lungs than the standard four-drug regimen, validating our *in vitro* work suggesting that SQ609 had positive interactions with these drugs.



In addition, SQ609 has the following attributes:

- Active against intracellular Mtb
- High specificity for Mtb
- Good aqueous solubility
- Orally bioavailable
- Favorable *in vitro* safety pharmacology and ADME profile, including:
  - High metabolic stability in human liver microsomes
  - Low inhibitory activity on individual cytochrome 450 enzymes
  - Low potency of binding to the vast majority of standard specific receptors and transporters
  - Low potency of K^+ channel blocker (HERG).

Next steps. A scalable manufacturing process for SQ609 is defined. In order to enter clinical evaluation, SQ609 must be synthesized and evaluated in IND-directed toxicology and pharmacology studies.

Market for New TB Drugs. The combined U.S. and EU market only for treatment of TB and latent TB is estimated to be $400M. In the U.S., an estimated 15-30M people are latently infected with Mtb, approximately 450,000 of whom are treated or prophylaxed for TB annually. Worldwide, 2 billion people are latently infected with *M. tuberculosis* and there are nearly nine million active cases of TB.

Intellectual Property. Sequella has an issued patent for SQ609 in the United States (10/441,272, filing date 5/19/2003). Corresponding patents in Australia, Canada, China, Eurasia, EPO, India, Japan, Singapore, and South Africa are issued or being prosecuted.

References. Copies of all referenced papers are available upon request: please contact katherinesacksteder@sequella.com.

1. Bogatcheva E, Hanrahan C, Chen P, et al. Discovery of dipiperidines as new antitubercular agents. Bioorg Med Chem Lett 2010;20:201-5.

2. Bogatcheva E, Hanrahan C, Nikonenko B, et al. Identification of SQ609 as a lead compound from a library of dipiperidines. Bioorg Med Chem Lett 2011;21:5353-7.